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Pretreatment Neutrophil-to-Lymphocyte Ratio in Endometrial Cancer: Association with Adverse Pathology and Advanced Stage but Not Overall Survival — A Single-Centre Cohort Study

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Abstract

Background

We examined the associations of pretreatment neutrophil-to-lymphocyte ratio (NLR) with adverse pathological features and advanced stage in surgically staged endometrial cancer, whether these associations were independent of established clinicopathological factors (tumour grade and depth of myometrial invasion), and whether NLR predicts overall survival.

Methods

254 consecutive women who underwent comprehensive surgical staging for endometrial carcinoma at a single tertiary centre (2018–2021) were reviewed. Pretreatment NLR was compared across pathological subgroups using non-parametric tests. Five multivariable logistic regression models were fitted—for LVSI, cervical stromal involvement, serosal/adnexal involvement, deep myometrial invasion and advanced stage (FIGO ≥ III)—adjusted for age, BMI, tumour grade and, where applicable, depth of myometrial invasion. Discrimination for advanced stage was assessed by ROC analysis; the incremental value of NLR beyond tumour grade and depth of myometrial invasion was tested with nested logistic models (change in AUC by DeLong, integrated discrimination improvement, and likelihood-ratio testing); and overall survival was compared between groups dichotomised at the cohort median NLR.

Results

A total of 254 patients were analysed (mean age 62.9 years; mean NLR 2.78; mean follow-up 38.5 months). After adjustment for age, body mass index, tumour grade and depth of myometrial invasion, NLR was independently associated with LVSI (aOR 1.42, 95% CI 1.12–1.81), serosal/adnexal involvement (aOR 1.72, 1.15–2.57), deep myometrial invasion (aOR 1.31, 1.06–1.62) and advanced stage (FIGO ≥ III; aOR 1.60, 1.23–2.08), but not with cervical stromal involvement (aOR 1.21, p = 0.196). Beyond these associations, adding NLR to a base model of tumour grade and myometrial invasion significantly improved discrimination of advanced stage (AUC 0.721 → 0.774; ΔAUC + 0.053, 95% CI 0.007–0.104; integrated discrimination improvement [IDI] 0.062, 95% CI 0.012–0.141; likelihood-ratio p < 0.001), whereas its incremental value for the individual adverse pathological features was modest and inconsistent (for serosal/adnexal involvement, likelihood-ratio p = 0.007 but ΔAUC and IDI non-significant). NLR did not predict overall survival (three-year survival 93.7% vs 88.9%, log-rank p = 0.116).

Conclusions

Pretreatment NLR was independently associated with adverse pathological features and advanced stage but did not predict overall survival, in contrast to earlier reports. Its contribution beyond established

clinicopathological factors was selective, being significant for advanced stage yet modest and inconsistent for the individual pathological features; in exploratory analyses serum CA-125 added more than NLR, and the two combined performed best. These findings define a limited and specific role for NLR rather than confirming it as a prognostic marker, and warrant prospective validation, including alongside molecular classification.

Background

Endometrial cancer (EC) is the most frequent gynaecological malignancy in developed countries and its incidence has been climbing steadily for two decades, in step with the rise in obesity and the ageing of the population [1, 2]. In Turkey, age-standardised incidence rates have roughly doubled since the early 2000s [3]. Surgical staging, with hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings and pelvic with or without para-aortic lymph node assessment (or sentinel mapping), still drives most decisions on adjuvant treatment [4]. Pathological factors that consistently predict recurrence include deep myometrial invasion, high tumour grade, non-endometrioid histology, lymphovascular space invasion (LVSI), cervical stromal involvement and extension to the serosa or adnexa [5–7]. The 2021 ESGO/ESTRO/ESP guidelines [4] added the four molecular subgroups of The Cancer Genome Atlas, namely POLEmut, MMRd, p53abn and NSMP, to this classical framework [8]; the FIGO 2023 staging system has since incorporated both LVSI and molecular subtype into stage assignment [9].

In unselected series, POLEmut tumours (5–10%) carry an excellent prognosis with dense lymphocytic infiltration; MMRd tumours (25–30%) are also lymphocyte-rich; p53abn tumours (10–15%) have an immunosuppressive microenvironment and the worst outcome; and NSMP tumours (50–60%) behave heterogeneously with generally low immune infiltrate [10, 11]. Turkish studies have shown that the surrogate ProMisE classification can be applied in routine practice, though universal molecular profiling remains beyond the reach of many institutions [12].

Even where molecular results can be obtained, they are rarely available before primary surgery. For this reason a preoperative biomarker derived from routine blood tests that complements pathological work-up is of practical interest. The neutrophil-to-lymphocyte ratio (NLR), calculated from a routine complete blood count, has been studied for this purpose. NLR reflects the balance between innate, tumour-promoting inflammation and the adaptive, tumour-suppressing lymphocytic response [13, 14]. Tumour-associated neutrophils release matrix metalloproteinases, neutrophil extracellular traps and pro-angiogenic factors, while peripheral lymphopenia indicates impaired cytotoxic T-cell activity [15]. The expected inflammatory phenotype is not the same across molecular subgroups: POLEmut and MMRd tumours mount strong adaptive responses, whereas p53abn tumours are associated with PD-L1-positive macrophages and exhausted T cells, a profile compatible with higher peripheral NLR values [16, 17].

In other solid tumours, including colorectal, gastric, ovarian and cervical cancer, an elevated pretreatment NLR has been linked to worse survival [18–20]. In endometrial cancer specifically, the meta-analysis by Ni et al. of 3,390 patients reported pooled hazard ratios of 2.22 for overall survival and

1.81 for progression-free survival in NLR-high patients [21], and a later synthesis by Leng et al. reached comparable conclusions but pointed out wide variation in cut-offs (1.9 to 3.0) and patient selection [22]. Critically, whether NLR adds information beyond the established clinicopathological factors already used for risk stratification—rather than merely correlating with them—has rarely been formally tested, even though this incremental value is what determines clinical usefulness.

The present study was therefore designed to move beyond simple association and to ask, in a Turkish single-centre cohort of comprehensively staged patients, whether pretreatment NLR adds incremental value over established clinicopathological factors—tumour grade and depth of myometrial invasion—for identifying adverse surgical-pathological features and advanced stage, and whether it predicts overall survival. The incremental contribution was quantified with nested logistic models using the change in area under the curve, the integrated discrimination improvement and likelihood-ratio testing.

Methods

Study design and patient selection

This was a single-centre retrospective cohort study. The electronic medical record system of the Department of Obstetrics and Gynecology, İzmir Katip Çelebi University, Atatürk Training and Research Hospital, İzmir, Turkey, was searched for all consecutive patients who underwent comprehensive surgical staging for histologically confirmed EC between 1 January 2018 and 31 December 2021. Two hundred and fifty-four patients with complete demographic, laboratory, surgical-pathological and follow-up data were enrolled. Follow-up data were extracted up to the most recent recorded outpatient or oncology visit through April 2025.

Inclusion criteria were: (i) histologically confirmed primary endometrial carcinoma; (ii) complete pretreatment haemogram obtained within seven days prior to surgery; and (iii) comprehensive surgical staging performed at our institution. Exclusion criteria were: (i) prior neoadjuvant chemotherapy or radiotherapy; (ii) active infection, autoimmune disease, haematological malignancy or recent (< 4 weeks) corticosteroid use; (iii) synchronous malignancy; and (iv) incomplete staging or insufficient follow-up data.

The study was conducted in accordance with the Declaration of Helsinki. Institutional ethics committee approval was obtained from the İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (decision number 27–185/2026), and the requirement for written informed consent was waived because of the retrospective and anonymised nature of the analysis.

Surgical staging and histopathological assessment

Comprehensive surgical staging consisted of exploration of the abdominal cavity; collection of peritoneal washings; biopsy of any suspicious peritoneal lesion; total abdominal hysterectomy with

bilateral salpingo-oophorectomy; omental biopsy; and bilateral pelvic ± para-aortic lymphadenectomy. All hysterectomy specimens were examined by two dedicated gynaecological pathologists at the institutional Department of Pathology. Disease was staged according to the FIGO 2009 system, which was the standard during the study period. Histological type was classified as endometrioid or non-endometrioid (serous, clear cell, mucinous, mixed and carcinosarcoma). Tumour grade was assigned using the FIGO three-tier system. LVSI was recorded as a binary variable (positive/negative); the WHO 2020 three-tier system (none/focal/substantial) was not consistently reported during the study period, and retrospective reassessment on archived slides was not feasible for the full cohort.

Laboratory measurements and definition of NLR

All patients had a complete blood count performed within seven days before surgery, in the absence of clinically apparent infection. Absolute neutrophil and lymphocyte counts were obtained from automated cell counters. The NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count. The optimal cut-off for NLR was determined by receiver operating characteristic (ROC) analysis using the Youden index, with advanced-stage disease (FIGO stage ≥ III) as the dichotomous outcome. For survival analyses, the cohort median NLR (2.55) was used as a pre-specified dichotomisation threshold.

The ROC-derived Youden threshold (2.20) was optimised for discrimination of advanced-stage disease and was therefore outcome-specific; to avoid overfitting the survival analysis to a discrimination-derived cut-off, the pre-specified cohort median NLR (2.55) was used for the Kaplan–Meier comparison.

Statistical analysis

Continuous variables are summarised as mean ± standard deviation or median (interquartile range, IQR) according to their distribution, and categorical variables as counts and percentages. The distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Because NLR and the other inflammatory indices were not normally distributed, non-parametric methods were used for all ratio-based comparisons. Analyses were performed on complete cases.

Median NLR was compared across each surgical-pathological subgroup using the Mann–Whitney U test for binary variables and the Kruskal–Wallis test for variables with more than two categories, with median (IQR) reported per subgroup. The ability of NLR to discriminate advanced-stage disease (FIGO ≥ III) was assessed by ROC analysis, reporting the area under the curve (AUC) with its 95% confidence interval (CI) computed by the DeLong method, together with sensitivity and specificity at the optimal Youden cut-off.

Five surgical-pathological outcomes were each entered into a separate multivariable binary logistic regression: the three features significant on univariable analysis—lymphovascular space invasion (LVSI), cervical stromal involvement and serosal/adnexal involvement—together with deep myometrial invasion and advanced stage (FIGO ≥ III). NLR was modelled as a continuous variable; covariates pre-specified on

clinical grounds were age (continuous), body mass index (continuous), tumour grade (ordinal, 1/2/3) and depth of myometrial invasion (≥ 50% vs < 50%); depth of myometrial invasion was omitted from the model in which it was itself the outcome. Results are reported as adjusted odds ratios (aOR) with 95% CIs, and the number of events per variable was examined for each model.

Incremental value was defined as improved discrimination and model fit when NLR was added to a model already containing the established clinicopathological predictors. For each of cervical stromal involvement, serosal/adnexal involvement, deep myometrial invasion and advanced stage, a base model (tumour grade, depth of myometrial invasion, age and body mass index) was compared with the same model plus NLR in a nested, sequential fashion. The incremental contribution was quantified by the change in AUC (ΔAUC) with the DeLong test, a nested likelihood-ratio test, and the integrated discrimination improvement (IDI); 95% confidence intervals for ΔAUC and IDI were obtained by the percentile bootstrap with 1,000 resamples. The potential clinical utility of adding NLR, alone and together with serum CA-125, to the base model was explored by decision curve analysis, plotting net benefit against threshold probability for advanced stage.

Because the serosal/adnexal outcome was infrequent, all logistic models were additionally re-estimated using Firth's penalized-likelihood method to reduce small-sample and separation bias, and concordance with the standard estimates is reported. A further sensitivity analysis was restricted to endometrioid tumours.

From the same preoperative complete blood count, the platelet-to-lymphocyte ratio (PLR = platelet/lymphocyte), monocyte-to-lymphocyte ratio (MLR = monocyte/lymphocyte) and systemic immune-inflammation index (SII = platelet × neutrophil/lymphocyte) were derived and examined within the same univariable framework. These analyses were pre-specified as exploratory and are reported as supplementary, intended to indicate which ratio tracks which pathological feature. In a further exploratory analysis confined to advanced stage, NLR was combined with PLR, MLR, SII and log-transformed serum CA-125 in the same nested framework to assess whether any combination improved discrimination over the clinicopathological base.

Overall survival was estimated by the Kaplan–Meier method, with patients dichotomised at the cohort median NLR and compared using the log-rank test. Three-year overall survival is reported for each group with its 95% CI, and the number at risk at 36 months is stated to convey the precision of the landmark estimate; the available follow-up did not support a five-year landmark.

The primary pathological models were pre-specified and hypothesis-driven; no formal correction for multiple comparisons was applied, and the exploratory composite-index analyses are interpreted with this in mind. Analyses were performed in SPSS version 20.0 (IBM Corp., Armonk, NY, USA), MedCalc version 12 (MedCalc Software, Ostend, Belgium) for ROC and DeLong curve comparisons, and R (logistf for Firth regression, pROC for DeLong tests, and PredictABEL/nricens for IDI). A two-sided $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient characteristics are summarised in Table 1. The 254 patients had a mean age of 62.9 years, a mean body mass index of 30.9 kg/m² and a mean pretreatment NLR of 2.78, with a mean follow-up of 38.5 months.

Table 1
Demographic, clinical and laboratory characteristics of the study cohort (n = 254).

Variable	Minimum	Maximum	Mean ± SD
Age (years)	38	85	62.9 ± 10.5
BMI (kg/m²)	18.5	48.0	30.9 ± 5.0
Neutrophils (×10⁹/L)	2.40	11.36	5.59 ± 1.82
Lymphocytes (×10⁹/L)	0.75	3.92	2.18 ± 0.51
Platelets (×10⁹/L)	140	506	287.1 ± 70.2
Monocytes (×10⁹/L)	0.20	1.06	0.56 ± 0.16
NLR	0.74	8.56	2.78 ± 1.33
PLR	50.4	468.5	141.0 ± 56.7
MLR	0.06	1.15	0.27 ± 0.12
SII	156	2355	795.7 ± 434.0
Follow-up (months)	2.1	60.4	38.5 ± 9.0

BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SD, standard deviation.

Surgical-pathological findings

Surgical-pathological findings are detailed in Table 2. Most tumours were endometrioid (85.8%); deep myometrial invasion was present in 35.0%, LVSI in 26.8%, cervical stromal involvement in 12.2% and serosal/adnexal involvement in 5.9%. Advanced-stage disease (FIGO ≥ III) was present in 43 patients (16.9%), the remaining 211 (83.1%) being stage I–II (stage II, n = 16).

Table 2
Distribution of postoperative surgical-pathological findings (n = 254).

Variable	Category	n (%)
Myometrial invasion	< 50%	165 (65.0)
	≥ 50%	89 (35.0)
Lymphovascular space invasion	Positive	68 (26.8)
	Negative	186 (73.2)
Cervical stromal involvement	Positive	31 (12.2)
	Negative	223 (87.8)
Serosal and/or adnexal involvement	Positive	15 (5.9)
	Negative	239 (94.1)
Histological type	Endometrioid	218 (85.8)
	Non-endometrioid	36 (14.2)
Tumour grade	Grade 1	124 (48.8)
	Grade 2	101 (39.8)
	Grade 3	29 (11.4)
FIGO 2009 stage	I–II	211 (83.1)
	≥ III	43 (16.9)

FIGO, International Federation of Gynecology and Obstetrics (2009 staging system).

Association of NLR with pathological features

Median NLR values by pathological subgroup are presented in Table 3 and Fig. 1. On univariable comparison, NLR was significantly higher with LVSI, cervical stromal involvement, serosal/adnexal involvement, deep myometrial invasion, advanced FIGO stage and higher tumour grade (all $p \leq 0.003$), and was lower in endometrioid than non-endometrioid tumours ($p = 0.018$). The exploratory PLR, MLR and SII followed a broadly similar pattern (Supplementary Table S1).

Table 3
Distribution of pretreatment NLR according to surgical-pathological findings.

Variable	Category	NLR median (IQR)	p value
Myometrial invasion	< 50%	2.42 (1.75–3.20)	0.003*
	≥ 50%	2.84 (2.06–3.70)	
Lymphovascular space invasion	Negative	2.42 (1.73–3.19)	< 0.001*
	Positive	3.10 (2.27–4.26)	
Cervical stromal involvement	Negative	2.47 (1.76–3.29)	0.002*
	Positive	2.98 (2.58–4.03)	
Serosal/adnexal involvement	Negative	2.50 (1.79–3.28)	0.001*
	Positive	3.70 (3.01–5.14)	
Histological type	Endometrioid	2.50 (1.79–3.27)	0.018*
	Non-endometrioid	3.09 (2.18–4.05)	
Tumour grade	Grade 1	2.42 (1.68–3.21)	< 0.001*
	Grade 2	2.50 (1.84–3.42)	
	Grade 3	3.36 (2.81–4.30)	
FIGO stage	I–II	2.43 (1.69–3.22)	< 0.001*
	≥ III	3.22 (2.61–4.30)	

*IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio. * Statistically significant (p < 0.05). p values from Mann–Whitney U (binary variables) or Kruskal–Wallis (grade) tests. Exploratory PLR, MLR and SII results are provided in Supplementary Table S1.*

Multivariable logistic regression analyses

Results of the five multivariable models are shown in Table 4 and Fig. 2. After adjustment for age, body mass index, tumour grade and depth of myometrial invasion, pretreatment NLR was independently associated with LVSI (aOR 1.42, 95% CI 1.12–1.81), serosal/adnexal involvement (aOR 1.72, 1.15–2.57), deep myometrial invasion (aOR 1.31, 1.06–1.62) and advanced stage (FIGO ≥ III; aOR 1.60, 1.23–2.08), but not with cervical stromal involvement (aOR 1.21, 0.91–1.61; p = 0.196), for which tumour grade was the dominant covariate. Tumour grade was the only covariate significant across all models, and Firth-penalized estimates were concordant throughout.

Table 4
Multivariable logistic regression of pretreatment NLR for four adverse pathological features and advanced stage.

Outcome	Covariate	aOR (95% CI)	p value
LVSI	NLR (per 1-unit)	1.42 (1.12–1.81)	0.004*
	Age (per year)	1.03 (1.00–1.06)	0.072
	BMI (per kg/m²)	1.04 (0.98–1.11)	0.196
	Grade (per level)	3.18 (1.98–5.10)	< 0.001*
	Myometrial invasion ≥ 50%	1.09 (0.57–2.10)	0.797
Cervical stromal involvement	NLR (per 1-unit)	1.21 (0.91–1.61)	0.196
	Age (per year)	1.01 (0.98–1.06)	0.486
	BMI (per kg/m²)	1.00 (0.92–1.09)	0.953
	Grade (per level)	3.65 (2.01–6.63)	< 0.001*
	Myometrial invasion ≥ 50%	1.13 (0.48–2.63)	0.783
Serosal/adnexal involvement	NLR (per 1-unit)	1.72 (1.15–2.57)	0.008*
	Age (per year)	0.97 (0.92–1.03)	0.287
	BMI (per kg/m²)	1.03 (0.91–1.16)	0.638
	Grade (per level)	5.88 (2.40–14.42)	< 0.001*
	Myometrial invasion ≥ 50%	0.40 (0.11–1.51)	0.175
Deep myometrial invasion (≥ 50%)	NLR (per 1-unit)	1.31 (1.06–1.62)	0.012*
	Age (per year)	1.00 (0.97–1.03)	0.912
	BMI (per kg/m²)	1.03 (0.98–1.09)	0.241
	Grade (per level)	1.88 (1.26–2.80)	0.002*
Advanced stage (FIGO ≥ III)	NLR (per 1-unit)	1.60 (1.23–2.08)	< 0.001*
	Age (per year)	1.02 (0.98–1.06)	0.307

*aOR, adjusted odds ratio; CI, confidence interval; LVSI, lymphovascular space invasion; NLR, neutrophil-to-lymphocyte ratio. * Statistically significant (p < 0.05). Each outcome was modelled independently, with NLR entered as a continuous variable and adjusted for age, BMI, tumour grade and depth of myometrial invasion. Firth-penalized estimates for NLR were concordant (LVSI 1.40, 95% CI 1.10–1.78; cervical stromal 1.20, 0.91–1.59; serosal/adnexal 1.66, 1.14–2.42; deep myometrial invasion 1.30, 1.05–1.61; advanced stage 1.57, 1.21–2.03).*

Outcome	Covariate	aOR (95% CI)	p value
	BMI (per kg/m²)	1.05 (0.98–1.13)	0.163
	Grade (per level)	2.04 (1.23–3.37)	0.006*
	Myometrial invasion ≥ 50%	1.38 (0.66–2.90)	0.396

*aOR, adjusted odds ratio; CI, confidence interval; LVSI, lymphovascular space invasion; NLR, neutrophil-to-lymphocyte ratio. * Statistically significant (p < 0.05). Each outcome was modelled independently, with NLR entered as a continuous variable and adjusted for age, BMI, tumour grade and depth of myometrial invasion. Firth-penalized estimates for NLR were concordant (LVSI 1.40, 95% CI 1.10–1.78; cervical stromal 1.20, 0.91–1.59; serosal/adnexal 1.66, 1.14–2.42; deep myometrial invasion 1.30, 1.05–1.61; advanced stage 1.57, 1.21–2.03).*

The incremental value of NLR over the base clinicopathological model was outcome-dependent. Adding NLR significantly improved both model fit and discrimination for advanced stage (likelihood-ratio p < 0.001; AUC 0.721 → 0.774; ΔAUC + 0.053, 95% CI 0.007–0.104; IDI 0.062, 95% CI 0.012–0.141, both bootstrap intervals excluding zero), whereas the gain was smaller for deep myometrial invasion and serosal/adnexal involvement and negligible for cervical stromal involvement. In a sensitivity analysis restricted to endometrioid tumours, the NLR associations with cervical stromal and serosal/adnexal involvement were attenuated and non-significant, reflecting the smaller number of events.

In exploratory analyses confined to advanced stage, we examined whether combining NLR with the other routinely available markers improved discrimination beyond the grade-and-myometrial-invasion base (Fig. 3, Supplementary Table S2). Among single markers, log-transformed serum CA-125 added the most (ΔAUC + 0.085, 95% CI 0.033–0.151; IDI 0.149), whereas the platelet- and monocyte-to-lymphocyte ratios added little. Combining NLR with CA-125 improved discrimination beyond either alone (AUC 0.833, 95% CI 0.783–0.907; ΔAUC + 0.112, 95% CI 0.049–0.182; IDI 0.216), while adding all four ratios together with CA-125 produced only a marginal further gain at the cost of model complexity (nine covariates for 43 events). These combination analyses are exploratory and, given the limited number of events, require external validation.

Decision curve analysis for advanced stage is shown in Fig. 4. Across the clinically plausible range of threshold probabilities (approximately 10–40%), the base-plus-NLR and base-plus-NLR-plus-CA-125 models both yielded positive net benefit, exceeding the treat-all and treat-none strategies, with the combined model generally providing the highest net benefit; the increment over the base clinicopathological model was modest. In keeping with the discrimination analyses, this decision-analytic signal is exploratory and, given the small number of events, requires confirmation in larger cohorts.

Discriminative performance and overall survival

ROC analysis for advanced-stage disease (FIGO ≥ III) yielded an AUC of 0.722 (95% CI 0.648–0.795, p < 0.001), indicating moderate discrimination. The optimal Youden cut-off was NLR > 2.20, providing 93.0% sensitivity and 42.7% specificity (Fig. 5).

Three-year overall survival did not differ significantly between patients dichotomised at the median NLR (2.55): 93.7% (95% CI 89.5–97.9) for NLR < 2.55 versus 88.9% (95% CI 83.4–94.4) for NLR ≥ 2.55 (log-rank p = 0.116). There were 28 deaths overall (10 vs 18); median overall survival was not reached in either group, and the numbers at risk at 36 months were 109 and 104, respectively (Fig. 6).

Discussion

Principal findings and biological interpretation

In this single-centre retrospective cohort of 254 comprehensively staged patients with EC, pretreatment NLR was significantly associated on univariable analysis with several adverse pathological features, including LVSI, cervical stromal involvement, serosal/adnexal involvement, deep myometrial invasion, high tumour grade and advanced stage. After adjustment for age, body mass index, tumour grade and depth of myometrial invasion, NLR remained independently associated with LVSI, serosal/adnexal involvement, deep myometrial invasion and advanced stage (FIGO ≥ III), whereas its association with cervical stromal involvement was attenuated by tumour grade and no longer significant. NLR discriminated advanced-stage disease with moderate accuracy (AUC 0.722, p < 0.001) but did not predict overall survival. When formally tested against tumour grade and depth of myometrial invasion, NLR added significant incremental value for advanced stage (both the change in AUC and the integrated discrimination improvement were significant), but only modest and inconsistent incremental value for the individual pathological features. This pattern is compatible with NLR reflecting aspects of the tumour–host inflammatory interaction relevant to local and extra-uterine disease extension, rather than acting as a standalone prognosticator.

The independent association between elevated NLR and LVSI is biologically plausible. LVSI represents the earliest morphological correlate of haematogenous and lymphatic dissemination and has been confirmed as an independent predictor of distant recurrence and reduced survival in early-stage endometrioid EC, including in a recent multi-institutional analysis of 3,546 patients (LySEC) which demonstrated hazard ratios of 1.8 for disease-free survival and 2.1 for overall survival [23]. Tumour-associated neutrophils, recruited by chemokines such as CXCL8/IL-8 secreted by stromally invasive tumour cells, may facilitate LVSI through release of matrix metalloproteinases, neutrophil extracellular traps and pro-angiogenic factors [14, 24]. Our finding that NLR remained an independent correlate of LVSI after adjustment is consistent with this mechanism and with prior reports by Suh et al. and Wang et al. [25, 26]. Of note, although deep myometrial invasion was associated with LVSI on univariable analysis (OR 1.85, 95% CI 1.05–3.27), it did not retain independent significance in the multivariable model (aOR 1.09, p = 0.797); tumour grade, which is closely correlated with invasion depth, appeared to absorb this signal. This contrasts with the LySEC cohort, in which deep myometrial invasion, high grade, cervical

stromal involvement and tumour diameter ≥ 2 cm were each independent predictors of LVSI [23], and may reflect grade–invasion collinearity and the modest size of our cohort rather than a genuine biological divergence.

Cervical stromal involvement, which determines FIGO stage II and is itself an independent risk factor for nodal dissemination [27, 28], was associated with elevated NLR on univariable comparison (p = 0.002), corroborating the earlier report of Wang et al., who described NLR as an independent preoperative predictor of cervical stromal involvement (OR 3.10, 95% CI 1.10–8.76) [26]. In our larger cohort, however, this association did not persist after adjustment for tumour grade (aOR 1.21, p = 0.196), suggesting that the cervical-stromal signal is largely explained by grade rather than by NLR itself. In contrast, the association between NLR and serosal/adnexal involvement remained independent (aOR 1.72), aligning with the concept that systemic inflammation accompanies extra-uterine spread; the incremental value of NLR over grade and myometrial invasion for this outcome, though statistically detectable on the likelihood-ratio test, was quantitatively modest.

Unlike several previous studies—including the meta-analyses by Ni et al. [21] and Leng et al. [22], which reported pooled hazard ratios of approximately 2.0 for both overall and progression-free survival—we did not observe a significant survival difference between NLR-high and NLR-low patients (three-year overall survival 93.7% vs 88.9%, log-rank p = 0.116). Several factors may account for this. First, the cohort median (NLR 2.55) was used as the dichotomisation threshold; published cut-offs range from 1.9 to 3.0, and the choice of cut-off materially affects survival comparisons. Second, the predominance of early-stage (FIGO I) disease (83.1%) yields a relatively low event rate (28 deaths), limiting statistical power for survival analyses. Third, the mean follow-up of approximately three years captures early recurrences but limits detection of late events. Our null survival finding contrasts with a recent single-centre cohort of 398 patients, in which an elevated NLR (cut-off 2.27) remained an independent predictor of overall survival [29]; this divergence most likely reflects differences in cut-off selection, case-mix, event rate and follow-up length, whereas the associations we captured at the level of the resected specimen remain evident.

Interpreted across outcomes, the added value of NLR is concentrated in advanced stage rather than in prognosis: when tested formally against tumour grade and depth of myometrial invasion, NLR improved discrimination of advanced stage, whereas for the individual pathological features it largely overlapped with grade. In exploratory combination analyses confined to advanced stage, discrimination improved further when NLR was combined with serum CA-125, while the platelet- and monocyte-to-lymphocyte ratios added little (Supplementary Table S2); this pattern is consistent with NLR and CA-125 capturing partly complementary information rather than with either alone being sufficient. In an era in which the ESGO/ESTRO/ESP guidelines [4] have integrated molecular classification (POLEmut, MMRd, p53abn, NSMP) with classical pathological features, simple inflammatory markers should be evaluated for their incremental value when added to existing risk algorithms rather than tested in isolation. Building on these observations, future studies should test whether NLR—alone or combined with serum CA-125—adds to preoperative risk-stratification scores such as those of Bendifallah and AlHilli [30, 31].

Two features frame the contribution of the present study. First, whereas most prior work has related single inflammatory ratios to survival or lymph-node metastasis, the association of NLR with serosal and/or adnexal involvement has, to our knowledge, not been specifically characterised; our data are therefore compatible with NLR acting mainly as a marker of local and extra-uterine extension rather than as a survival predictor. Second, the field has increasingly moved from single ratios towards composite indices—including the platelet-to-lymphocyte and monocyte-to-lymphocyte ratios and the systemic immune-inflammation index—and towards nomograms that combine these with CA-125 and pathological variables, an approach that has achieved high discrimination for nodal metastasis [32]. In our exploratory analysis these composite indices tracked the same features as NLR, suggesting they capture overlapping inflammatory signals; whether any retains independent, incremental value once established predictors are accounted for remains to be determined.

Our findings also refine the pattern reported by Muangto et al., who in a single-centre Thai cohort found elevated preoperative NLR associated with adverse clinicopathological features and PLR as an independent predictor of deep myometrial invasion. In our cohort both NLR and PLR were higher with deep myometrial invasion on univariable testing ($p = 0.003$ and $p = 0.002$); we therefore did not reproduce a clean NLR–PLR dissociation, suggesting that these correlated ratios capture overlapping inflammatory signals rather than distinct dimensions of tumour biology [33].

These observations are best interpreted against the wider role of NLR across malignancies. A landmark meta-analysis of more than 100 studies established an elevated NLR as an adverse prognostic marker across solid tumours, while showing that the optimal cut-off varies widely between series [34]. Within gynaecological oncology the signal appears tumour-type dependent: in cervical cancer, a meta-analysis of 6,041 patients found pretreatment NLR to be an independent predictor of overall and progression-free survival [35]. Our predominantly early-stage endometrial cohort fits this broader inflammation–cancer paradigm at the level of adverse pathology and stage, yet, unlike the survival signal reported in cervical cancer and in earlier endometrial meta-analyses [21, 22], showed no survival difference, underscoring that the prognostic weight of NLR depends on tumour type, disease stage and the chosen cut-off.

Molecular context and future directions

Because molecular profiling was not performed in this cohort, the relationship between NLR and ProMisE subgroups cannot be tested here and any inference remains hypothesis-generating. The four subgroups display distinct inflammatory phenotypes: POLEmut and MMRd tumours are typically immune-rich, NSMP tumours show low immune infiltrate, and p53abn tumours have been described as immunosuppressive [14, 16, 17]. On theoretical grounds, peripheral NLR might therefore be highest in p53abn-type disease, but this expectation has not been formally tested in a Turkish cohort. Our observation of pathological associations without a corresponding survival difference is consistent with molecular heterogeneity within the LVSI-positive group, which spans all four ProMisE subgroups including prognostically favourable POLEmut tumours [16, 23]. Prospective multicentre studies with full ProMisE stratification will be needed to establish whether NLR adds value to existing risk algorithms.

Clinical implications

Pretreatment NLR is inexpensive, derived from a routine complete blood count and available before any intervention, which positions it as a potential preoperative adjunct rather than a replacement for pathological or molecular assessment. Within the limits of this exploratory analysis, its value was concentrated in flagging advanced stage, and its discrimination improved when it was combined with serum CA-125—another marker already obtained during routine preoperative work-up. In settings where molecular classification or dedicated pelvic imaging is not readily available, a simple combination of an inflammatory ratio and a tumour marker of this kind could, if validated, help identify patients who merit more extensive staging or referral to a gynaecological-oncology centre. These are hypothesis-generating observations from a single-centre cohort with few events, and prospective external validation is required before any clinical application.

Strengths and limitations

The strengths of this study include the relatively large, single-centre, comprehensively staged cohort with central pathology review by two dedicated gynaecological pathologists, and a complete, contemporary follow-up window. Several limitations should also be acknowledged. First, the retrospective single-centre design carries inherent selection and information biases, and external validation in independent cohorts is required. Second, molecular classification (POLE/MMR/p53/NSMP) was not performed during the study period and could not be incorporated; this is the single most important limitation in light of contemporary risk-stratification frameworks. Third, FIGO 2009 staging was used because the FIGO 2023 revision was published after the close of recruitment, and retrospective re-staging was not attempted, since that system requires molecular subtype and standardised WHO 2020 three-tier LVSI assessment, neither of which was available for the full cohort. Fourth, LVSI was consequently recorded only as a binary variable. Fifth, peritoneal cytology, although still reported, no longer affects FIGO staging. Sixth, NLR was measured only once preoperatively; although patients with clinically evident infection, autoimmune disease, corticosteroid use or haematological disorders were excluded, a single measurement may not fully capture chronic tumour-related inflammation or exclude transient non-tumour triggers such as perioperative anxiety or subclinical thrombosis. Seventh, preoperative pelvic MRI and transvaginal ultrasound findings were not recorded in a standardised format and could not be compared with NLR, so the incremental value of NLR over routine imaging remains to be established prospectively. Finally, the mean follow-up of approximately three years is sufficient to capture early recurrences but precludes reliable five-year survival estimation; the survival analysis was restricted to overall survival, as disease-free and disease-specific data were not uniformly available, and longer follow-up of this cohort is planned.

Conclusions

In this single-centre Turkish cohort, pretreatment NLR was independently associated with LVSI, serosal/adnexal involvement, deep myometrial invasion and advanced stage (FIGO ≥ III) after adjustment

for clinicopathological covariates, but not with cervical stromal involvement, which was explained by tumour grade. Notably, NLR did not predict overall survival, in contrast to earlier meta-analyses. When formally tested against established clinicopathological factors, its added contribution was selective: significant for the preoperative recognition of advanced stage (both the change in AUC and the integrated discrimination improvement were significant) but limited for the individual pathological features. In exploratory analyses, serum CA-125 added more than NLR and the two combined performed best, indicating that NLR is not sufficient on its own. Whether it retains incremental value alongside the ProMisE molecular classification within contemporary ESGO/ESTRO/ESP and FIGO 2023 frameworks warrants prospective multicentre evaluation.

Abbreviations

EC endometrial cancer
NLR neutrophil
to-lymphocyte ratio
PLR platelet
to-lymphocyte ratio
MLR monocyte
to-lymphocyte ratio
SII systemic immune
inflammation index
LVSI lymphovascular space invasion
CA
125 cancer antigen 125
AUC area under the receiver operating characteristic curve
ΔAUC change in area under the curve
IDI integrated discrimination improvement
CI confidence interval
OS overall survival
IQR interquartile range
SD standard deviation
BMI body mass index
ROC receiver operating characteristic
FIGO International Federation of Gynecology and Obstetrics
ESGO European Society of Gynaecological Oncology
ESTRO European Society for Radiotherapy and Oncology
ESP European Society of Pathology
ProMisE Proactive Molecular Risk Classifier for Endometrial Cancer.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (decision number 27-185/2026). As the study was a retrospective analysis of de-identified medical records, the requirement for written informed consent was waived by the same committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available owing to institutional data-protection requirements but are available from the corresponding author on reasonable request, subject to institutional and ethical approvals.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

S.Ş. and A.Y. designed the study, performed the staging operations from which the cohort was assembled, and collected the clinical data. S.Ş. analysed the data and wrote the first draft. A.Y. contributed to the surgical pathology review and to data verification. M.Ş. and F.G.Ş. assisted with chart review, follow-up data extraction and reference work. All authors read and approved the final manuscript.

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Figures

Figure 3. Pretreatment NLR distribution stratified by adverse pathological features

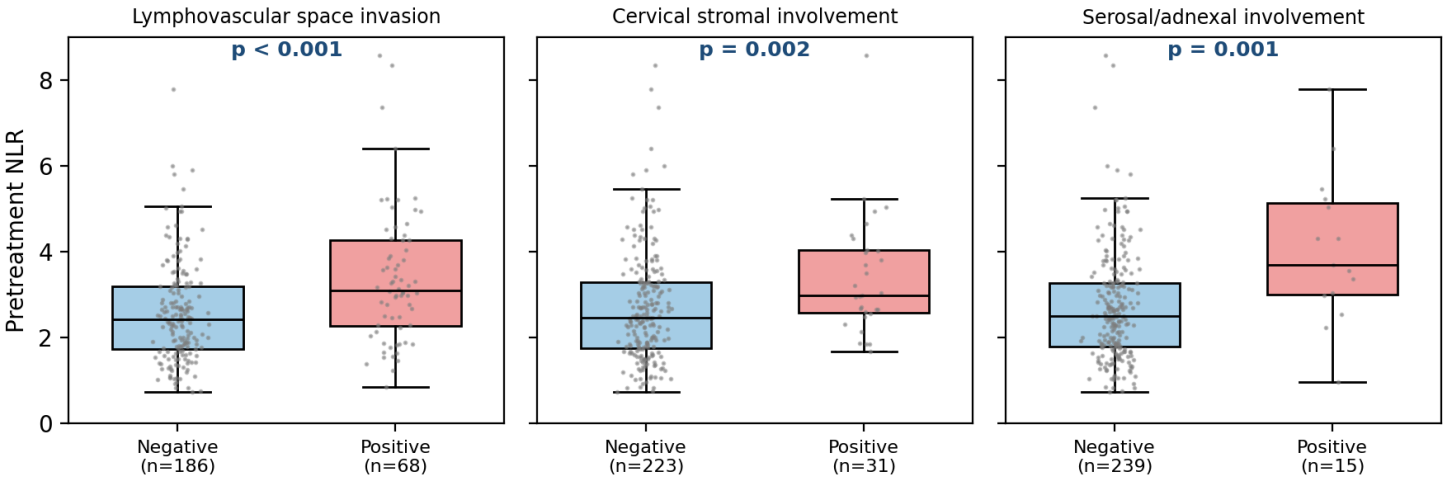


Figure 1

Box plots of pretreatment NLR distribution stratified by lymphovascular space invasion (left, p < 0.001), cervical stromal involvement (centre, p = 0.002) and serosal/adnexal involvement (right, p = 0.001). Boxes show the median and interquartile range; whiskers extend to 1.5 × IQR. Individual data points are overlaid as grey markers. Comparisons by Mann–Whitney U test.

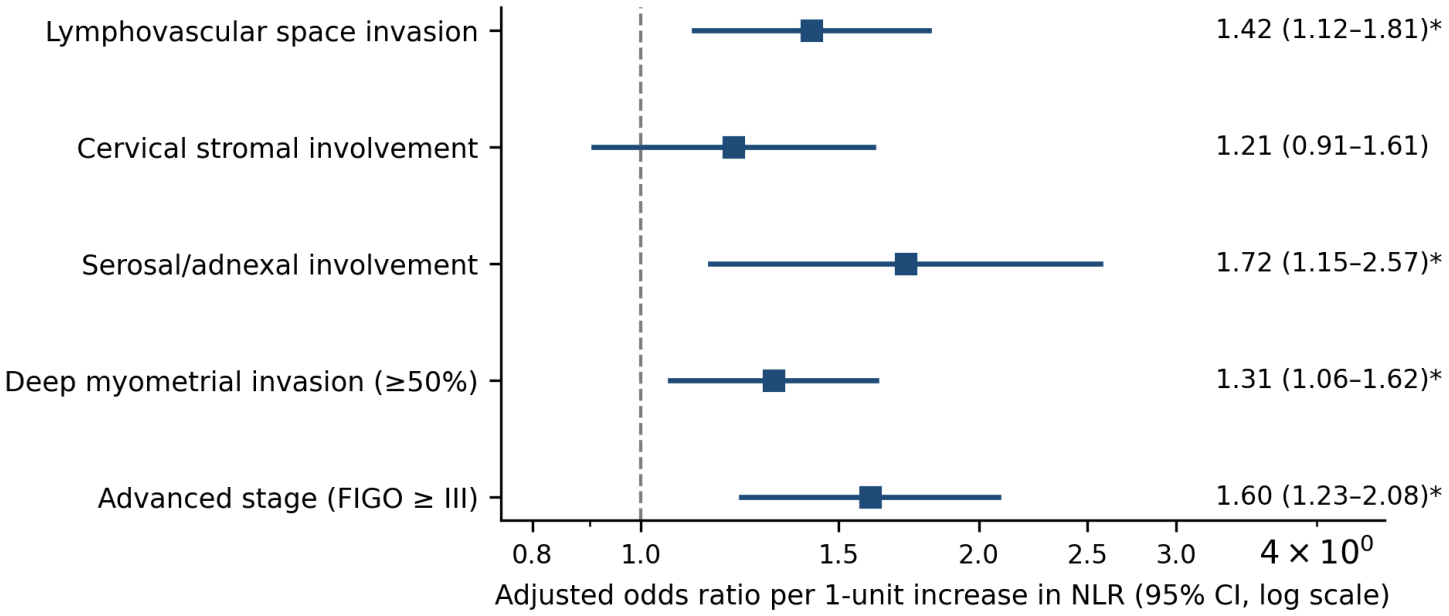


Figure 2

Forest plot of adjusted odds ratios (aOR) for a 1-unit increase in pretreatment NLR across the five multivariable logistic regression models: lymphovascular space invasion, cervical stromal involvement, serosal/adnexal involvement, deep myometrial invasion and advanced stage (FIGO ≥ III). Squares denote point estimates and horizontal lines the 95% confidence intervals; the dashed vertical line marks the null value (aOR = 1.0). NLR was independently associated with every outcome except cervical stromal involvement (asterisk, $p < 0.05$). The horizontal axis is shown on a logarithmic scale.

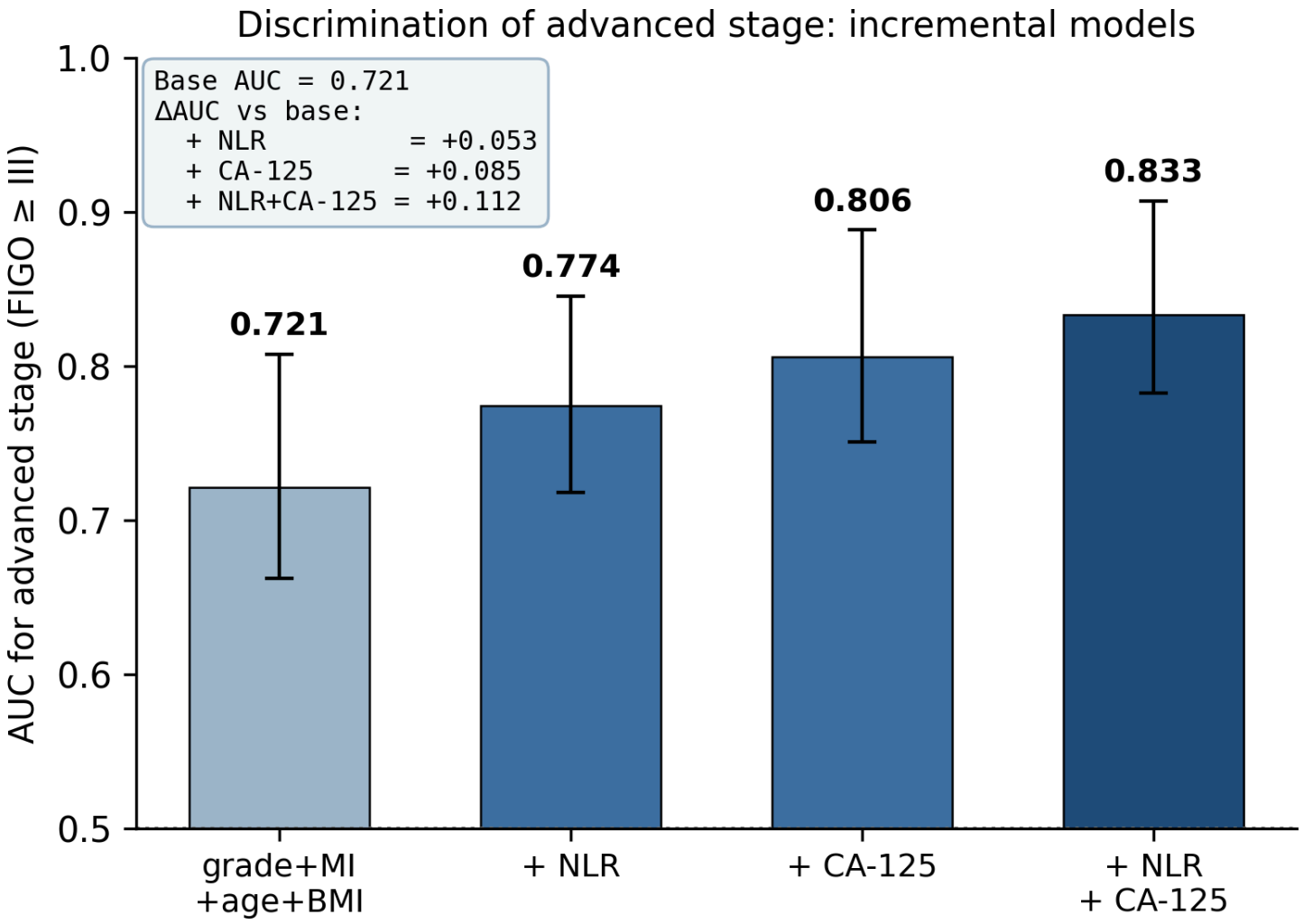


Figure 3

Discrimination (area under the ROC curve, AUC) for advanced-stage disease (FIGO 2009 stage ≥ III) of the base clinicopathological model (tumour grade, depth of myometrial invasion, age and body mass index) and of the same model with pretreatment NLR, serum CA-125 (log-transformed) and both markers added. Bars show the AUC; whiskers denote 95% confidence intervals obtained by the percentile bootstrap (1,000 resamples). The dotted line marks chance discrimination (AUC 0.5). These combination analyses are exploratory.

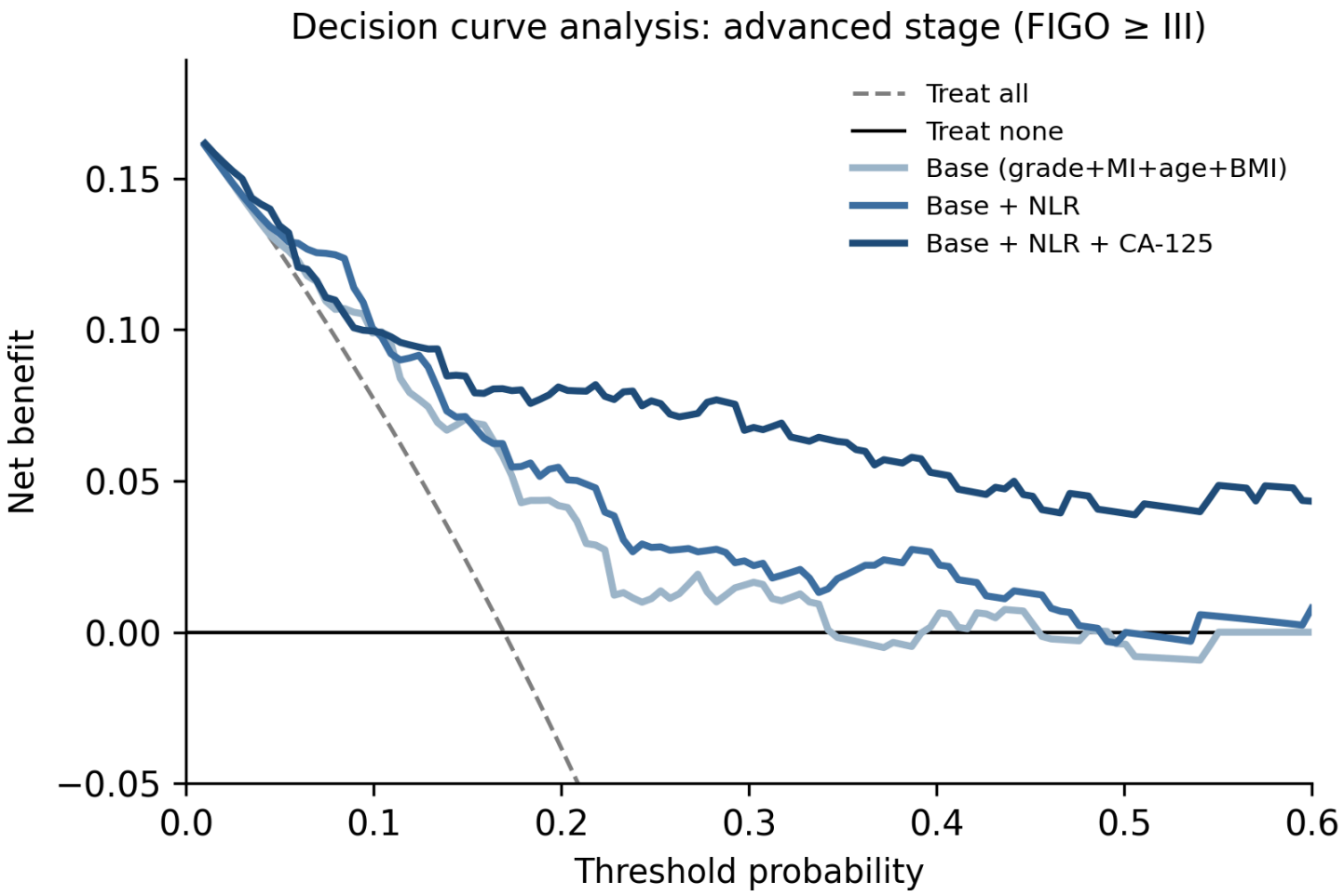


Figure 4

Decision curve analysis for advanced-stage disease (FIGO 2009 stage ≥ III). Net benefit is plotted against the threshold probability for the base clinicopathological model (tumour grade, depth of myometrial invasion, age and body mass index), the base model plus pretreatment NLR, and the base model plus NLR and serum CA-125, together with the treat-all (grey dashed) and treat-none (horizontal) reference strategies. Curves lying above the reference strategies indicate positive net benefit. This analysis is exploratory.

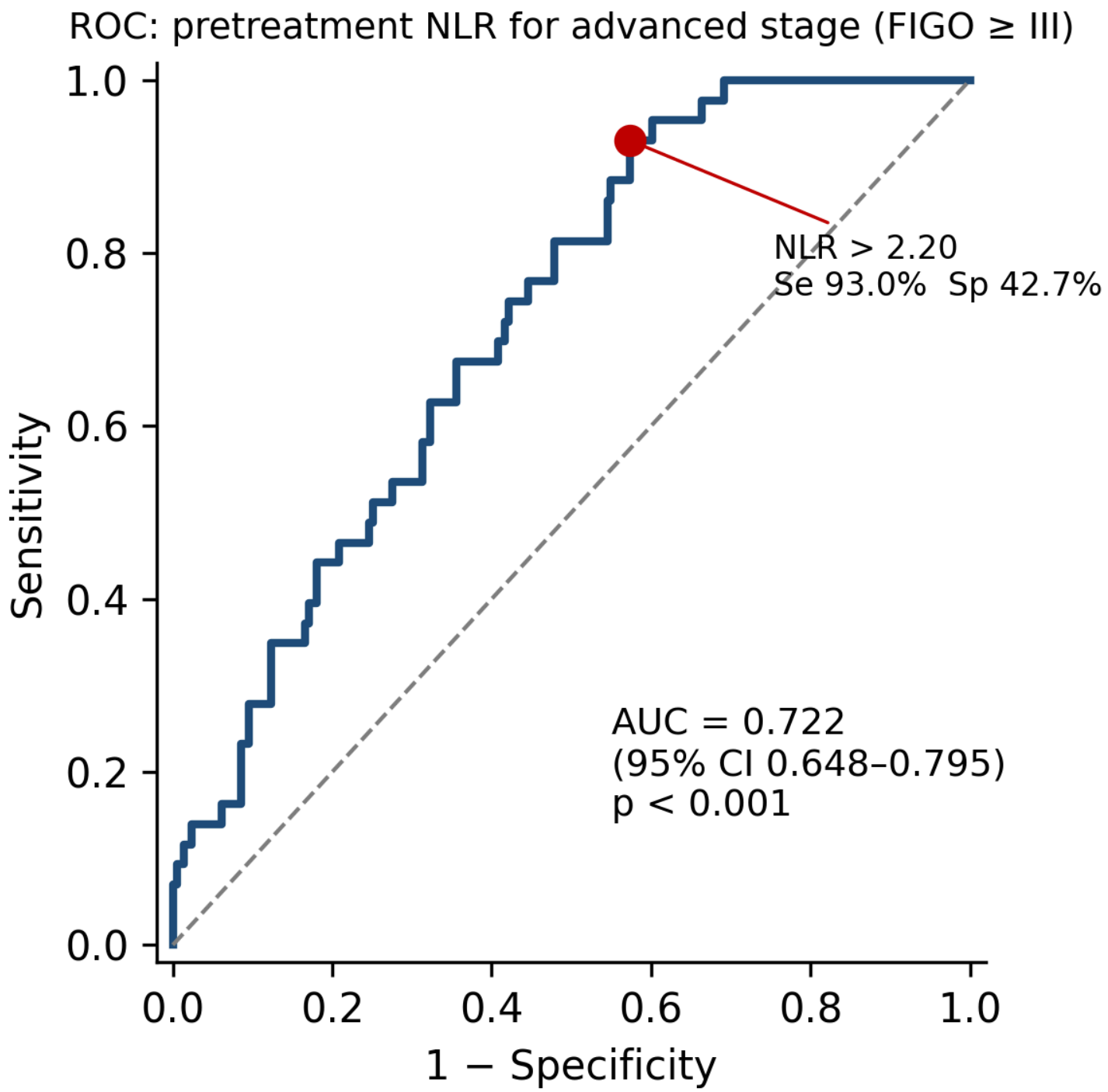


Figure 5

Receiver operating characteristic (ROC) curve of pretreatment NLR for advanced-stage endometrial cancer (FIGO ≥ III). Area under the curve (AUC) = 0.722 (95% CI 0.648–0.795, p < 0.001). The optimal Youden cut-off was NLR > 2.20 (sensitivity 93.0%, specificity 42.7%; red marker). The diagonal reference line indicates chance performance.

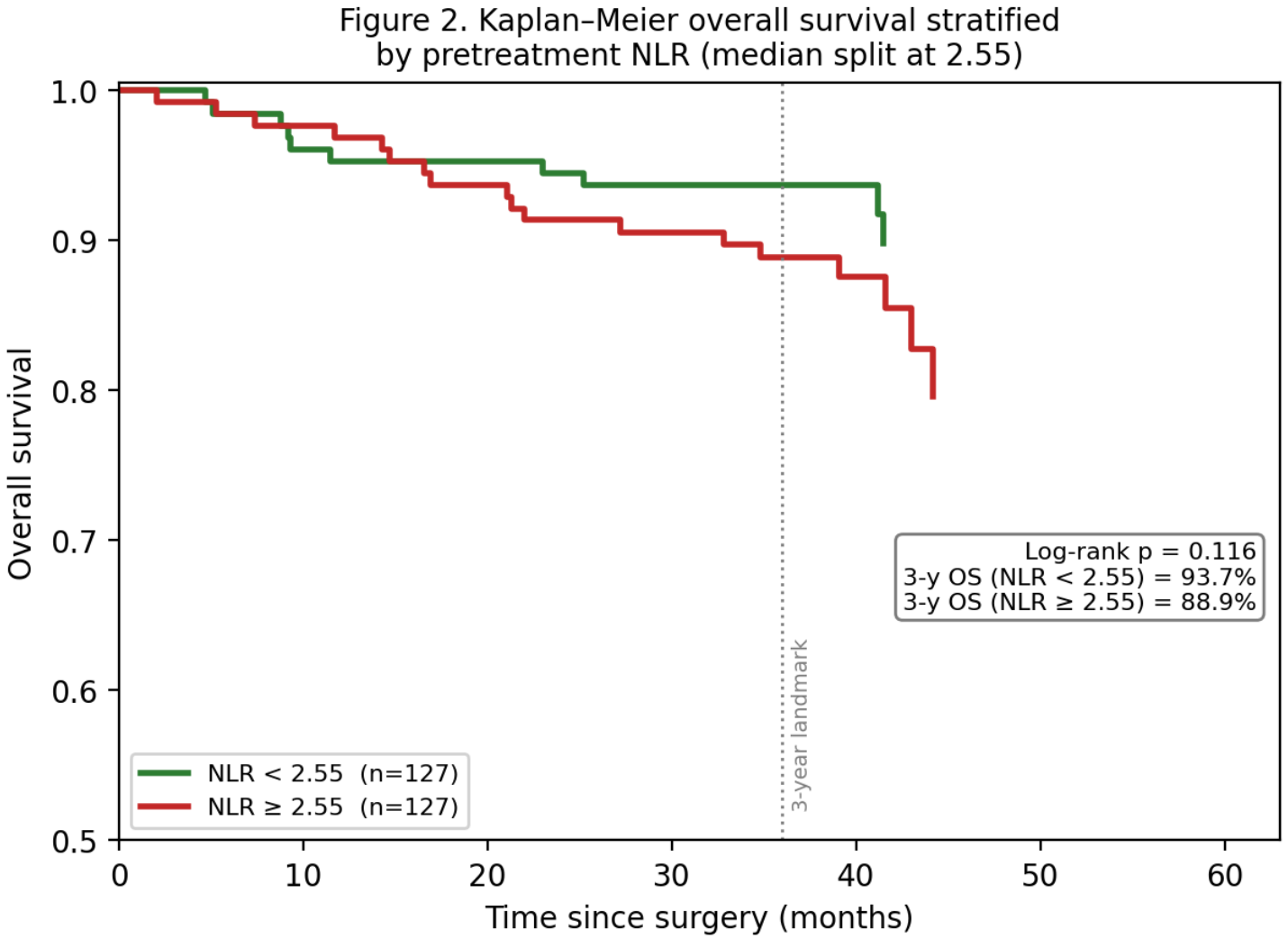


Figure 6

Kaplan–Meier estimates of overall survival in 254 patients with endometrial cancer, stratified by pretreatment NLR using the cohort median (2.55) as the dichotomisation threshold. Three-year overall survival was 93.7% (95% CI 89.5–97.9) in the NLR < 2.55 group versus 88.9% (95% CI 83.4–94.4) in the NLR ≥ 2.55 group (log-rank p = 0.116). The vertical dotted line marks the three-year landmark.

Supplementary Files

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